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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/717,450	NEUHOLD ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-57,59-77 and 79-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-57,59-77 and 79-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 8-9-04 have been fully considered but they are not persuasive. Claims 58 and 78 have been cancelled. Claim 97 has been added. Claims 55-57, 59-77 and 79-97 are pending and under consideration in the instant office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

An initialed copy of the IDS filed 8-9-04 is attached hereto.

Claim Rejections - 35 USC § 112 – written description

Claims 55-57, 59-77 and 79-96 remain rejected and claim 97 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "joint-specific promoter" lacks written description because the specification does not disclose any promoters that meet the description of "joint-specific promoters" provided in the specification other than the type II collagen promoter. The specification defines "joint-specific expression" as expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% (pg 15, lines 19-20). Such promoters include the Type II collagen promoter (pg 16, line 3). However, the specification and the art do not teach any promoters other than

the Type II collagen promoter that cause expression greater in joints than other tissues or causes expression in non-joint tissues is less than 10%. Despite the fact that applicants defined the genus, describing the structure of one species within the genus fails to describe the genus as a whole. Adequate written description of a "joint-specific promoter" requires more than a mere statement that it is part of the invention. What is required is a description of a reasonable number of promoters having that function. Defining what applicants consider the function of a "joint-specific promoter" without describing the structure of promoters having that function is simply a wish to identity promoters having that function. Naming a promoter that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Applicants argue any promoter that functions in the joint can be used in the instant invention (pg 27 of arguments). Applicants' argument is moot because the claims do not encompass using any promoter that functions in a joint. The claims are limited to using "joint-specific promoters" which are defined in the specification by their function: providing expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10%. The definition of "joint-specific promoters" in the specification does not encompass any promoter that functions in the joint.

Applicants argue the specification adequately satisfies the written description requirement by providing an explicit description in words of this generic invention, and through examples of the invention's ability to degrade collagen in both spatial (joint) and temporal (inducible) regulation in an animal (pg 19, 1st full ¶ of arguments). Applicants argue the examiner's basis for the rejection is flawed because the specification fully

describes joint specific promoters in explicit language (pg 19, 2nd full ¶ of arguments). Applicants cite pg 16, lines 7-13; pg 15, line 19 through pg 16, line 9; pg 6, lines 15-20 and pg 36, line 21- pg 37, line 1; Examples 4 and 5. Applicants' arguments are not persuasive.

Pg 16, lines 7-13, merely describes the function of the promoter as being "joint-specific" (the transcriptional activator polypeptide under the control of a joint-specific promoter...."

Pg 15, line 19, though pg 16, line 9, merely defines the function of "joint-specific promoters" ("Promoters that direct transcription selectively in joint tissues. Joint-specific expression as used herein refers to expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% of the level of expression in joints. Preferably, expression in non-joint tissues is undetectable. Useful promoter sequences that confer joint-specific expression on a sequence to which they are operably linked to include without limitation sequences derived from the collagen type II promoter"). The specification only describes the structure of one promoter having the function defined in the specification. Describing the structure of one species within a genus defined by function is not adequate written description of other structures within the genus. Other promoters that meet the definition on pg 15, lines 19, through pg 16, line 9 may not exist.

Pg 6, lines 15-20, refers to "joint-specific promoters", specifically type II collagen promoter, but does not describe the structure of any other promoters having the same function.

Pg 36, lines 21, through pg 37, line 1, refers to a "joint-specific promoter (type II collagen", but does not describe the structure of any other promoters having the same function.

Pg 40, lines 1-22, Example 4 describes obtaining "joint specific expression conferred by type II collagen promoter" but does not describe any promoter other than type II collagen promoter having such function.

Defining the function of what applicants consider "joint-specific promoters" without describing the structure of adequate numbers of promoters having that function is simply a wish to identity promoters having that function. Defining the function of a promoter without describing the structure of a representative number of promoters having that function or comparing the structure of type II collagen promoter to other promoters, is not adequate description of "joint-specific promoters." Type II collagen promoter may be the only promoter that meets applicants definition of "joint-specific promoter." As such the specification does not adequately describe the structure of a representative number of species within the genus (defined by function).

Applicants argue "joint-specific promoters" were well known in the art (pg 20, 1st full ¶ of arguments). Applicants' argument is unfounded. Applicants state, "[a]s set forth in the Second Neuhold Declaration... ...the specific promoter employed to achieve tissue specific expression does not make any difference" but do not teach any other promoters known in the art that meet applicants' definition of "joint-specific promoters". The second Neuhold declaration, ¶ 7, merely states the identity of other promoters within the genus "is not important." The declaration states the CD-RAP/MIA promoter may be substituted for the type II collagen promoter (¶ 7); however, the CD-RAP/MIA promoter did not meet the functional definition of "joint-specific promoter" provided in the specification, i.e. providing expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10%. Applicants' arguments regarding 5,625,124; 5,880,327; 5,917,123; 6,028,245 are moot because

each patent is examined on its own merits and because none of the patents show that other promoters meeting applicants' definition of "joint-specific promoters."

Applicants argue that a "representative number of examples serves as an adequate written description of a genus in the absence of an express description of the genus." Applicants cite *Regents of the University of California v. Eli Lilly,* 119 F.3d 559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The board found "a description of the genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" (¶ bridging pg 20-21 of arguments). Applicants' arguments are not persuasive.

Applicants have described the structure of one species within the genus of "joint-specific promoters" defined in the specification by their function. The board found that providing the structure of a representative number of cDNAs having a common function is enough to claim a genus using functional language not explicit in the specification as originally filed. Unlike the facts presented to the Board in *Eli Lilly*, applicants have failed to provide adequate written description for "joint-specific promoters" because 1) applicants have defined the genus by function but have only provided the structure of one species within the genus, and 2) the specification does not provide structural features common to a substantial portion of the members of the genus. Defining the genus of "joint-specific promoters" by function without providing a representative number of species by structure or structural features common to the members of the genus is not adequate written description of the genus.

Applicants argue the broader concept of the mice in the claims overcomes the lack of written description of the narrower concept of "joint-specific promoters" used to

make the mice (pg 21, 1st full ¶). Applicants' argument is not persuasive. Without adequately describing the elements used to make the mice, the specification cannot adequately describe the mouse. The mouse claimed does not have adequate written description because "joint-specific promoters" used to make the mice (other than type II collagen promoter) do not have adequate written description.

Applicants argue identification of "other perhaps as yet undisclosed promoter that provides for joint-specific expression... ...makes no difference as to the claimed invention" pg 21, 2nd full ¶. Applicants' argument is not persuasive. Claiming a genus of promoters, while wishing to know other promoters within the genus, is at the heart of the law. The wish to know promoters within a genus defined by function without providing a representative number of examples by structure or structural features common to the members of the genus fails to meet the description requirements.

Applicants argue, "generation of transgenic animals is routine, and their phenotype predictable" (pg 24 of arguments). as support, applicants point to pg 22, line 15, to pg 26, line 8; pg 17, line 21 through pg 18, line 6, of the specification, which teaches a method of making transgenic mice and suggest using the method to make other species of transgenics. The Neuhold Declaration, ¶ 9, states that in 1996, "creation of transgenic mammals required no more than ordinary technical efforts." Applicants' argument is not persuasive. Applicants' arguments fail to address the fact that different species may not be capable of having the phenotype claimed. If the phenotype is not possible in other species, no amount of screening would allow for one of skill to obtain the desired phenotype in any mammal as broadly claimed. One species within the genus is not adequate written description of the genus because the common structural element (the transgene) would be greatly influenced by the host

genome and would not be expected to have the same function in any non-human mammal as broadly claimed.

Claim Rejections - 35 USC § 112 – enablement

Claims 54-57, 59-77 and 79-96 remain rejected and claim 97 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause degradation of type II collagen, does not reasonably provide enablement for any non-human mammal, or any "joint-specific promoter" as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

THE CLAIMS

The claims relate to a transgenic non-human mammal whose genome comprises DNA encoding a constitutively enzymatically active MMP that cleaves Type II collagen in a regulatable system capable of Type II collagen degradation during adulthood, methods of degrading Type II collagen in such a mammal, and methods related thereto. One of the regulatory proteins is under the control of a "joint-specific promoter."

Claims 55-57, 59-64, 66-77, 79 and 81-97 encompass transgenic non-human mammals or rats made using a "joint-specific promoter" and methods related thereto. Claims 65 and 80 are limited to transgenic non-human mammals or rats made using the type II collagen promoter.

Claims 54-57, 59-63, 67-71, 75-77 and 79-91, 93-97 encompass transgenic non-human mammals and methods related thereto. Claims 64-66, 72-74 and 92 are limited to transgenic rats and methods related thereto.

Claims 54-57, 59-61, 63-65, 67-70, 72, 73, 75-77 and 79-83, 85-87 require the MMP is capable of being expressed "to a level sufficient to cause Type II collagen degradation in the joints of the mammal."

Claims 62, 66, 71, 74, 84 and 88-96 require transgenic non-human mammals or rats in which the Type II collagen degradation obtained in the joints results in "a loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof."

STATE OF THE ART AND UNPREDICTABILITY

The state of the art at the time of filing was that it was unpredictable whether a desired phenotype could be obtained. The art also taught that one transgene could cause different phenotypes in different species of transgenics; therefore, the phenotype between species using the same transgene was unpredictable. For example, Mullins of record (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer of record (1990, Cell, Vol. 63, pg 1099-1112) described spontaneous

inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023, both of record) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the species-specific requirements for transgene design were not clearly understood, and the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain the desired phenotype was not within the realm of routine experimentation at the time of filing.

The art at the time of filing also taught that attempts to engineer transgenic animals expressing MMP1 and stromelysin, both of which were expected to degrade Type II collagen, did not cause joint degeneration. "[P]revious attempts to engineer transgenic animals expressing MMPs such as MMP-1 and stromelysin have not resulted in an observable joint degeneration phenotype in transgenic animals" (pg 4, line 15, of the instant specification).

Not only was the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing taught that transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice. Wall of record (1996, Theriogenology, Vol. 45, pg 57-68) taught that "position effect" and "unidentified control elements" "contribute to lack of transgene expression in some lines and variable expression in other lines." As a result, "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies" (¶ bridging pg 61-62).

Thus, uncontrollable factors may prevent the transgene from ever being expressed. If expression does occur, the resulting phenotype in mice may not occur in other species.

The art taught that obtaining expression of a transgene in different species does not necessarily result in the desired effect. Ebert of record (1988, Mol. Endocrinology, Vol. 2, pg 277-283) taught that a transgene encoding somatotropin could be used to express the protein in the blood of both transgenic mice and pigs. However, expression of the protein did not cause an increase in growth (the desired effect) in pigs (pg 277, col. 2, lines 17-27). Thus, expression of the protein does not guarantee a phenotype. Despite obtaining a mouse that expressed the transgene and caused the desired effect, it was unpredictable whether a non-mouse expressing the same transgene would have the desired phenotype at all.

Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest. The art at the time of filing did not teach any transgenic non-human mammal expressing an MMP that degrades Type II collagen or any other matrix-degrading enzyme.

Therefore, it was unpredictable whether a transgene encoding an MMP that degrades type II collagen known to degrade type II collagen in the joints of transgenic mice would be capable of degrading type II collagen in the joints in other non-human mammalian species, specifically in rats.

TEACHINGS AND EXAMPLES IN THE SPECIFICATION

The specification teaches making a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves

Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse. Expression is controlled by the administration/withdrawal of tetracycline or other regulatory compound.

"JOINT-SPECIFIC PROMOTER"

Claims 55-57, 59-64, 66-77, 79, 81-97 encompass transgenic non-human mammals or rats made using a "joint-specific promoter" and methods related thereto. Claims 65 and 80 are limited to transgenic non-human mammals or rats made using the type II collagen promoter.

Claims 55-57, 59-64, 66-77, 79, 81-97 are not enabled because the specification fails to provide adequate guidance so that one of skill could obtain and use any "joint-specific promoter" other than the type II collagen promoter to make the transgenic non-human mammals or rats claimed.

The specification defines "joint-specific expression" as expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% (pg 15, lines 19-20). Such promoters include the Type II collagen promoter (pg 16, line 3). However, the specification and the art do not teach the Type II collagen promoter causes expression greater in joints than other tissues or causes expression in non-joint tissues is less than 10%. Even if the Type II collagen promoter is "joint-specific" as defined in the specification, one species in the genus is not considered an

enabling disclosure of that genus. An enabling disclosure of a "joint-specific promoter" requires more than a mere statement that it is part of the invention. What is required is adequate guidance for one of skill to determine a reasonable number of promoters having that function without undue experimentation. Defining what applicants consider "joint-specific" without disclosing which promoters having that function, as in the instant case, is simply a wish to identity promoters having that function, and leaves the persons of skill with undue experimentation. Therefore, the phrase "joint-specific promoter" is not enabled.

OBTAINING MMP EXPRESSION "TO A LEVEL SUFFICIENT TO CAUSE TYPE II COLLAGEN DEGRADATION IN THE JOINTS" OF ANY "TRANSGENIC NON-HUMAN MAMMAL"

Claims 54-57, 59-63, 67-71, 75-77 and 79-91, 93-97 encompass any transgenic non-human mammal and methods related thereto. Claims 64-66, 72-74 and 92 are limited to transgenic rats expressing such MMP levels and methods related thereto.

Claims 54-57, 59-61, 63-65, 67-70, 72, 73, 75-77 and 79-83 and 85-87 require the transgenic non-human mammals or rats express MMP "to a level sufficient to cause Type II collagen degradation in the joints of the mammal."

Claims 62, 66, 71, 74, 84 and 88-96 require transgenic non-human mammals or rats in which the Type II collagen degradation obtained in the joints results in "a loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof."

Claims 54-57, 59-77 and 79-97 are not enabled because the specification fails to provide adequate guidance so that one of skill could obtain MMP expression to a level

sufficient to cause type II collagen degradation in the joints of any transgenic non-human mammal or rat as broadly claimed. More specifically claims 62, 66, 71, 74, 84 and 88-96 are not enabled because the specification fails to provide adequate guidance that MMP expression would cause a loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof in any transgenic non-human mammal or rat as broadly claimed.

Applicants suggest making other species of transgenics (pg 22-26) and teach how to screen transgenics for the desired phenotype (pg 40-44). Applicants do not provide adequate guidance for one of skill to predictably achieve MMP expression to a level sufficient to cause Type II collagen degradation in the joints of any mammalian species other than mice. Applicants do not provide adequate guidance for one of skill to overcome the art established unpredictability so that the expression of the MMP transgene would cause type II collagen degradation in the joints of any species. Merely screening animals of other species for the desired phenotype is not adequate to ensure that MMP expression will be of a level sufficient to cause type II collagen degradation in the joints of any species. That is because the desired phenotype may never occur in other species and because obtaining the phenotype in mice does not predict that the phenotype will occur in other species.

Applicants do not teach the level of Type II collagen degradation in the joints required to obtain a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, etc. Applicants do not teach the desired level of MMP expression required to obtain such phenotypes in any species or how to obtain the desired level of MMP expression. Without such

guidance, one of skill would not be able to control the level of MMP expression so that the level of MMP expression and the level of type II collagen degradation obtained was sufficient to obtain a loss of proteoglycan, cleave of type II collagen into a TCA degradation product, change joint function, change joint space narrowing, etc. Applicants do not provide adequate guidance for one of skill to control MMP expression and overcome the art established unpredictability so that a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, change joint function, change joint space narrowing, etc. would be predictably obtained in any species other than mice. Merely screening other species for the desired phenotype is not adequate to ensure that MMP expression and the amount of type II collagen degradation will be of a level sufficient to cause the claimed phenotype in any species. That is because the desired phenotype may never occur in other species and because obtaining the phenotype in mice does not predict that the phenotype will occur in other species.

Given the unpredictability in the art taken with the specification's example of a transgenic mouse that expresses MMP to a level sufficient to cause type II collagen and a method of screening for the desired phenotype taken with a mere suggestion to make transgenics of other species, it would require one of skill undue experimentation to ensure that any transgenic non-human mammalian as broadly claimed would express MMP to a level sufficient to cause Type II collagen degradation in the joints, especially such that type II collagen degradation in the joints caused a loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

ARGUMENTS

Applicants argue any promoter that functions in the joint can be used in the instant invention (pg 29 of arguments, 2nd full ¶). If that is the case, then the promoters used in the invention are not truly "joint-specific" as claimed. In fact, the promoters of the invention are not "joint-specific" as claimed because they are not generic to any tissue of the joint. The specification does not describe expressing MMP in any joint tissue other than chondrocytes. For example, the specification does not teach bone or blood vessels of a joint of the mouse claimed can express MMP such that collagen is degraded as claimed. The specification does not teach any bone, blood vessel or other joint-specific promoters that function in the instant invention. Applicants' reiterate previous arguments and point to other applications and other promoters, none of which would cause expression in the joint of the animal of the invention as required in the instant invention. No other "joint-specific" promoter that can express MMP and cause collagen degradation can be envisioned in the invention other than the Type II collagen promoter.

Applicants argue that MMPs and type II collagen were known to be highly conserved between species, that the MMPs in the claims must degrade type II collagen, that degradation of type II collagen in the claims results in cartilage damage, and that generation of transgenic animals was routine. Therefore, applicants conclude that it would have been predictable to express an MMP that degrades collagen type II in the joints of different species would results in the same phenotype, i.e. cartilage damage (pg 22, 1st full ¶, of arguments). The set of facts provided by applicants cannot lead one of skill to conclude that the phenotype found in mice could be obtained in other non-human mammals as broadly claimed when taken in view of the art established unpredictability in the art at the time of filing.

Applicants argue that one of skill could obtain and screen other transgenic non-human as broadly claimed until the phenotype claimed was found without undue experimentation. Applicants' arguments are not persuasive. The examiner has stet forth the art-established unpredictability in obtaining the desired phenotype in any non-human mammal. Applicants have failed to recognize that those who established the unpredictability of obtaining the desired phenotype in any non-human mammal were those of skill in the art – they also had the ability of making and screening other transgenic non-human mammals. However those of skill in the art recognized that the desired phenotype might not occur despite any amount of screening. Applicants have not provided any way for one of skill to overcome the art-established unpredictability so that the claimed phenotype would be predictable in any transgenic non-human mammal as broadly claimed. In particular, applicants fail to overcome the unpredictability described by Ebert, of record, who taught obtaining expression of a growth hormone transgene in different mammals; however, expression did not cause growth in all of the different mammals. Ebert screened numerous founder animals to come to such a conclusion. Thus, the desired phenotype may not be possible in every species even after obtaining expression of the transgene. Wall (1996) confirms this by teaching a transgene that functions in mice does not predictably function the same in other species or cause a desired effect because of position effects or unidentified control elements.

Applicants state Freije and Billinghurst taught sequence motifs are highly conserved between mammalian species, and are largely responsible for MMP activity" (pg 22 of arguments "MMPs are highly conserved across species"). Applicants' argument is not persuasive. Freije and Billinghurst did not teach that MMPs of any species that degrade type II collagen functions the same in other species. Applicants' assertion that Freije and Billinghurst taught the active site of MMPs that recognize type

II collagen are highly conserved between species is unfounded. No such teachings can be found in the art. More importantly, the conservation of MMPs that degrade type II collagen between species is irrelevant because the same protein may cause a different phenotype in mice and rats (Mullins 1989; Mullins 1990) and because the phenotype obtained in mice cannot be expected in other species using the same construct (Wall). Applicants have not provided adequate guidance for one of skill to predict that a construct encoding an MMP that degrades type II collagen will cause the same phenotype in any non-human mammal.

Applicants argue type II collagen is conserved between species. Applicants' argument is not persuasive. 80% homology between mice, rat, chicken, cow and human type II collagens (Cheah) is not adequate homology to conclude that any type II collagen could be cleaved by one specific MMP that degrades collagen, e.g. SEQ ID NO:1. More importantly, the conservation of type II collagen between species is irrelevant because expression of the transgene encoding an MMP that degrades type II collagen may not cleave type II collagen as expected (Mullins 1989; Mullins 1990), because expression of the MMP that degrades type II collagen may cause a different phenotype in mice and rats (Mullins 1989; Mullins 1990) and because the phenotype obtained in mice cannot be expected in other species using the same construct (Wall). Applicants have not provided adequate guidance for one of skill to predict that a construct encoding a specific MMP that degrades type II collagen will degrade any species of type II collagen and predictably cause the same phenotype in any non-human mammal.

Applicants argue degradation of type II collagen causes cartilage damage. Therefore, one of skill would predictably degrade type II collagen resulting in cartilage damage. Applicants' argument is not persuasive. First, the independent claims only

require degrading type II collagen and do not require cartilage damage. Second, some of the claims require more than just cartilage damage which may not be a common result of degrading any type II collagen, e.g. "loss of proteoglycan, cleavage of type II collagen into a TCA collagen degradation protein, a change in joint function..." (claim 62). Third, the fact that degradation of type II collagen causes cartilage damage is irrelevant because the type II collagen may be cleaved as expected, because expression of the MMP that degrades type II collagen may cause a different phenotype in mice and rats (Mullins 1989; Mullins 1990) and because the phenotype obtained in mice cannot be expected in other species using the same construct (Wall). Applicants have not provided any evidence that the same amounts of MMP expression were obtained in mice as well as another non-human mammal. Without such guidance, the specification does not enable one of skill to predict that a construct encoding an MMP that degrades type II collagen will degrade type II collagen or that expression of the MMP will predictably cause the same phenotype in any non-human mammal.

Applicants state the "Examiner has failed to provide any evidence that the transgenes utilized in the references cite (Ren-2 in Mullins 1990 and Mullins 1989; HLA-B27 in Hammer 1990 and Tuarog 1988) have any predictive value of the claimed transgenic mammals that express MMPs. Thus, these references are not indicative of non-enablement of the present invention." Applicants' argument is not persuasive. The examiner need not provide evidence that the animals that express Ren-2 and HLA-B27 genes are predictive of mammals that express MMPs that degrade collagen. The references show two examples where transgenes encoding materially distinct proteins caused different phenotypes in mice and rats. The references can be extrapolated to predicting the phenotype of transgenics made with transgenes encoding MMPs because they relate to two materially distinct proteins. No further evidence is required.

Applicants argue generation of transgenic animals is supported by the specification (pg 24, 2nd full ¶ of arguments). Applicants cite pg 22, line 15, through pg 26, line 8; pg 17, line 21, through pg 18, line 6. Applicants' arguments are not persuasive. Pg 22, line 15, through pg 26, line 8, does not teach how to isolate ES cells from species other than mice or how to overcome the art established unpredictability so the phenotype in mice would be expected in rats or other non-human mammals. Wall states, "[o]ur understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." Mullins 1990 and Mullins 1989 or Hammer 1990 and Taurog 1988 confirm this by comparing the phenotype of rats and mice using the same transgene. Wall also states "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies." Applicants have not provide any guidance for one of skill to overcome the art established unpredictability so that MMP expression would be predictably expected in species other than mice. Specifically, applicants have not addressed the "position effect" and "unidentified control elements" described by Wall that contribute to lack of transgene expression in some lines (pg 62, lines 1-3. Wall states transgenic farm animals will remain a challenge because experimentation will be required in the species of interest (pg 62, lines 6-7). It would have required one of skill in the art "undue experimentation" to determine how to control or alter a transgene that functioned in a mouse so that it had the same function in another species. Conservation of MMP and type II collagen would not ensure the MMP transgene that functioned in mice would be expressed in other species. The specification lacks any discussion as to how to overcome such obstacles or any correlation between transgenes known to function in mice and transgenes used in other

species. Without such guidance, the specification fails to overcome the unpredictability of obtaining expression of MMP in species other than mice.

Applicants argue the references cited support enablement (pg 25). Applicants argue different species of transgenics could easily be made and screened (pg 25, 2nd full ¶). Applicants' arguments are not persuasive. The transgene may not function in other species due to unknown position effects or control elements described by Wall and because Wall explicitly states a phenotype of a transgenic mouse do not predict the phenotype of a transgene in other species. Conservation of MMP and type II collagen between species does not ensure the MMP transgene that functioned in mice would be expressed in other species.

Applicants argue Cameron does not support the Examiner's assertion because Cameron does not correlate diversity of chromatin structure with species-specificity. Applicants argue Cameron supports the Applicants' assertion that it was routine to screen for transgenics that work. Applicants' arguments are not persuasive. Cameron clearly taught that the genetic diversity of different species of mice added to the unpredictability of the phenotype caused by a transgene. Cameron (1997, Molec. Biotechnol., Vol. 7, pg 253-265) taught expression of a transgene was unpredictable because of the insertion site of the transgene into the genome and the surrounding genetic background. Predictable levels of expression are not achieved because of the complete absence of expression or leaky expression in non-target tissues (pg 256, ¶ bridging col. 1-2). Factors causing variable expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (pg 256, col. 2, lines 3-9). These factors are copy number independent and integration site dependent, emphasizing the role the genetic background and site of integration in the level of expression of the transgene (pg 256,

lines 10-13). Thus, different strains of mice having the same transgene have different phenotypes. Increased genetic diversity caused increased, unpredictable differences in phenotype.

Applicants argue Mullins (1993) shows that creating a desired transgenic animal merely requires multiple trials with screening. Applicants' argument is not persuasive. Mullins (1993) cites the work of Mullins (1990) and Hammer (1990), who taught using a Ren-2 and HLA-B27 transgene, respectively, to make transgenic rats. These trials were preceded by Mullins (1989) and Taurog (1988), who taught using the ren-2 and HLA-B27 transgene, respectively, to make transgenic mice that did not have the desired phenotype (pg 631, col. 1, 1st ¶, of Mullins (1993)). No amount of screening would have caused the expected phenotype in every species.

Applicants argue Mullins (1989) shows that among successfully produced transgenic mice, variability of protein expression is expected. Therefore, applicants conclude that variability is irrelevant and that a variable level of success or even failure is a routine part of making transgenics. Applicants' arguments are not persuasive. Mullins (1990) states the mice of Mullins (1989) did not have the desired phenotype. Conducting more trials and continuing screening would not result necessarily result in a transgenic with the desired phenotype. Therefore, it would require undue experimentation for one of skill to determine how to alter the transgene or the integration of the transgene to obtain the desired phenotype in any species.

Applicants argue Taurog (1988) had failures that did not express the HLA-B27 molecule then obtained mice that did express the HLA-B27 molecule. Therefore, applicants conclude it was routine for such failures to occur and that eventual success could be obtained. Applicants' argument is not persuasive. Hammer (1990) states the mice of Taurog (1988) did not have the desired phenotype. Thus, conducting more

trials and continuing screening would not result necessarily result in the desired phenotype in every species. Therefore, it would require undue experimentation for one of skill to determine how to alter the transgene or the integration of the transgene to obtain the desired phenotype in every species.

Applicants argue Mullins (1996) reported that transgenic technology, including ES technology, was well established and described a number of non-mouse transgenic animal models. Applicants' arguments are not persuasive. Mullins (1996) was used to establish the state of the art of making transgenics and to establish that ES capable of providing germline transmission were not known in species other than mice. Mullins (1996) do not teach how to predictably obtain the desired phenotype in any species transgenic animal. Applicants have not provided guidance how to predictably obtain the desired phenotype in every species. Applicants have not taught how to obtain ES cells in species other than mice.

Applicants argue Ebert (1988) successfully generated transgenic animals for disease. Therefore, applicants conclude that failures are irrelevant because successes can be obtained. Applicants' argument is not persuasive. Ebert taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (pg 277, col. 2, lines 17-27). Applicants have not provided guidance how to overcome the unpredictably described by Ebert to obtain the desired phenotype in every species.

Applicants argue that Wall discusses transgenic non-mouse species. Therefore, applicants conclude that the examiner has erred in questioning the enablement of the invention. Applicants' argument is not persuasive. The examiner also has acknowledged that non-mouse species were known in the art. Applicants' argument does not address the basis of the rejection: one of skill would not have known how to

predictably obtain the desired phenotype in every species. The specification does not provide any guidance how to overcome such unpredictability. Applicants have not pointed to any references known at the time of filing that would have enabled one of skill to overcome such unpredictability. Applicants have not provided any evidence that any transgenic would express MMP that degrades type II collagen in their joints (see Ebert), that any amount of MMP (that degrades type II collagen) expression causes type II collagen degradation as claimed. Applicants have not provided any evidence that any amount of type II collagen degradation would cause the phenotypes listed in claims 62, 66, 71, 74, 84 and 88-96. The specification has not provided adequate guidance that MMP expression will be expressed in the joints of any, that the amount of expression obtained was the same as the amount obtained in mice, that the amount of expression obtained in mice was adequate to degrade type II collagen in every species, that the amount of expression required to degrade type II collage was the same in every species, that the amount of type II degradation required to cause the phenotypes listed in claims 62, 66, 71, 74, 84 and 88-96. Without such guidance, it would have required one of skill undue experimentation to overcome such unpredictability.

Applicants argue Overbeek showed different transgenic animals within a species had different levels of expression. Applicants point out that regulatory sequences help avoid variability (pg 97). Therefore, applicants conclude that failures and successes occur in the art of transgenic technology, and that screening for the successes is all that is required. Applicants' argument does not address the basis of the rejection: one of skill would not have known how to predictably obtain the desired phenotype in every species. The specification does not provide any guidance how to overcome such unpredictability for reasons in the paragraph above.

Applicants argue other unknown factors may have been responsible for the different results in Mullins (1989) and Mullins (1990). Applicants argue the phenotype in the instant application merely requires type II collagen degradation, which is different than the phenotype of Mullins (1989) and Mullins (1990) (hypertension). Therefore, applicants conclude that one of skill could have predicted that a transgenic animal expressing an MMP that degrades type II collagen would degrade type II collagen (pg 29, 2nd full ¶, of arguments). Applicants' arguments are not persuasive. One of skill could not predict that any transgenic would express MMP that degrades type II collagen in their joints (see Ebert). Applicants have not provided any evidence that any amount of MMP that degrades type II collagen expressed will causes type II collagen degradation as claimed. In addition, claims 62, 66, 71, 74, 84 and 88-96 encompass phenotypes that are dependent upon a certain amount of type II collagen degradation (i.e. change in joint function,, joint space narrowing, etc.). Applicants have not provided any evidence that any amount of type II collagen degradation would cause the phenotypes listed in claims 62, 66, 71, 74, 84 and 88-96. The specification has not provided adequate guidance that MMP expression will be expressed in the joints of any, that the amount of expression obtained was the same as the amount obtained in mice, that the amount of expression obtained in mice was adequate to degrade type II collagen in every species, that the amount of expression required to degrade type II collage was the same in every species, that the amount of type II degradation required to cause the phenotypes listed in claims 62, 66, 71, 74, 84 and 88-96. Without such guidance, it would have required one of skill undue experimentation to overcome such unpredictability.

Applicants argue that a lack of knowledge regarding the underlying disease mechanism of HLA-B27 disorders caused the unpredictability in Taurog (1988) and

Hammer (1990). Applicants argue the phenotype in the instant application merely requires type II collagen degradation, which is different than the phenotype of Taurog (1988) and Hammer (1990) (inflammatory disease). Therefore, applicants conclude that one of skill could have predicted that a transgenic animal expressing an MMP that degrades type II collagen would degrade type II collagen (¶ bridging pg 29-30 of arguments). Applicants' arguments are not persuasive for reasons in the above paragraph.

Applicants argue Taurog (1988), Hammer (1990), Mullins (1989) and Mullins (1990) cannot establish enablement because they were almost a decade before the invention (pg 30 of arguments). Applicants' argument is not persuasive. Applicants have not provided any evidence refuting the teachings of Taurog (1988), Hammer (1990), Mullins (1989) and Mullins (1990). Nor have applicants provided evidence where one transgene was known in the art to cause the same phenotype in two species. Applicants have not provided any evidence that expression of an MMP that degrades type II collagen with predictably "to a level sufficient to cause type II collagen degradation in the joints of the mammal" as claimed. Without evidence to the contrary, the teachings of Taurog (1988), Hammer (1990), Mullins (1989) and Mullins (1990) are considered valid and should be considered as the state of the art.

Regarding the second declaration of Dr. Neuhold:

The second declaration by Dr. Neuhold states generating transgenic animals having the desired feature was routine at the time of filing. The declaration refers to Bradley (1996, Nature Genetics, Vol. 14, pg 121) who states

> "For almost 15 years the methods for making transgenic mammals have remained virtually unchanged, consisting of the injection of naked DNA into the

> pronucleus of a fertilized egg. The technique is so reliable that the technical shortcomings can readily be circumvented by producing an excess of experimental material so that animals with the desired experimental outcome can be selected from a collection of founder mice[1]."
>
> 1. Palmiter (1985, Cell, Vol. 41, pg343-345).

Dr. Neuhold concludes ¶ 9 by stating that as of 1996, creation of transgenic mammals required no more than ordinary technical effects. Applicants' arguments are not persuasive. Bradley (1996) taught animals with the "desired experimental outcome" can be selected from a collection of founder mice. In context, Bradley (1996) merely discusses the ability to screen a collection of founder transgenics to determine founders that carried the transgene of interest. Bradley did not teach screening founder mice predictably resulted in identifying animals with the desired phenotype. Bradley did not teach how to make any mammals other than mice (see the citation at the end of the first sentence of Bradley, i.e. Palmiter, which only taught making transgenic mice). Bradley did not teach making non-mouse transgenics was routine. Bradley did not teach the phenotype obtained in transgenic mice predictably occurs in other mammals. The art taught phenotypes in mice do not occur in rats using the same construct (Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988) all of record). Mullins of record (1996, J. Clin. Invest. Vol. 98, pg S37-S40) taught transgene constructs react very differently from one species to another (pg S38, col. 1, last para.). Mullins (1993, Hypertension, Vol. 22, pp. 630-633) taught integration of a transgene into different species of animal gave divergent phenotypes. Ebert of record (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused

different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Wall of record (1996, Theriogenology, Vol. 45, pages 57-68) taught the physiological result of transgene expression in livestock was not predicted in transgenic mice (page 62, line 7). Therefore, the mere ability to make and screen transgenics that carry the transgene construct is not adequate for one of skill to predictably obtain the phenotype in mice in other mammalian species.

Dr. Neuhold states in ¶ 10 that the elements used in the mouse disclosed could be used in non-mouse species and "the only uncertainty remaining was to establish that this combination of features would cause phenotypic changes of osteoarthritis in a transgenic animal," which are described in the specification and could easily be screened for. Dr. Neuhold states in ¶ 11 that by teaching the combination of elements used to obtain the phenotype of interest in mice, there is a more than reasonable expectation of obtaining any transgenic mammal which will work better. Applicants' arguments are not persuasive. The specification, the declaration of Dr. Neuhold and Bradley (1996) do not adequately correlate the elements used in the disclosed mouse to other mammals such that the phenotype obtained in mice could be obtained in other mammals. The specification does not teach the level of expression of MMP and expression of the regulatory protein obtained in mice would be the same in other mammals using the same construct. The specification does not teach the Type II collagen promoter causes the same level of protein expression in mice and other mammals. The specification does not teach MMP degrades collagen to the same extent in mice and other mammals. The specification does not teach MMP causes the

same level of Type II collagen degradation cause the symptoms claimed in mice and other mammals. The specification does not teach the level of regulatory protein expressed that regulates MMP expression in mice is the same level required in other species. Without such guidance, taken with the unpredictability in the art, one of skill could not predict whether the phenotype in mice would occur in other species. Mere screening for a phenotype of interest would not allow one of skill in the art to predict whether the phenotype would occur in species other than mice.

Claim Rejections - 35 USC § 112 – indefiniteness

Claims 90-96 remain rejected and claim 97 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The previous rejection of claims 90-96 under indefiniteness has been withdrawn in view of the amendment.

However, claims 90-96 as newly amended are indefinite because the new phrase "providing a first and second transgenic non-human mammal of claim 55 in which a phenotypic change has been produced by activation of expression of the metalloproteinase at the same age during adulthood of the transgenic non-human mammals" is unclear. The step does not clearly set forth that the mammals express the MMP that degrades type II collagen to a level sufficient to cause type II collagen degradation in the joints, or that the mammals have type II collagen degradation in the joints. Specifically, the claims do not require that the mammals have "a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product..." as in the preamble of the claims. There appears to be a separate step in the phrase of

"activating" MMP expression in the first and second mammal during adulthood at the same time. However, as written, the step is not clearly set forth. The phrase "phenotypic change" in the "wherein any less extensive development in the nature or extent of the phenotypic change" lacks antecedent basis in view of the phrase "comparing the phenotype" in the step above. For this reason, the phrase "wherein any less..." does remains unclear regarding how to determine which compounds have potential to counteract degradation of type II collagen in joints of a transgenic non-human mammal as claimed.

The claims are free of the prior art of record.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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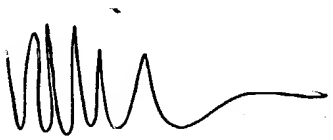
Michael C. Wilson



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